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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,378	03/24/2006	Kenya Shitara	00005.01290	4546

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EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,378	SHITARA ET AL.	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *22-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,29 and 30* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☒ Claim(s) *1-30* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/19/2006,10/22/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-21, 29, and 30 in the reply filed on 10/05/2007 is acknowledged. Applicant has further elected SEQ ID NO:5, 6, 7, for the VH region of the antibody and SEQ ID NO: 8, 9, and 10 for the VL region of the antibody in communication filed on 10/05/2007. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-19 and 22-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Status of Application, Amendments and/or Claims

The amendment of 03 March 2006 has been entered in full. Claims 2, 4, 5, 8-22, 24-28 have been amended. Claims 29 and 30 have been added.

Claims 1-13, 20, 21, 29, and 30 are pending and under examination.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The disclosure is objected to because of the following informalities: Applicants need to update the status of the parent applications in the first line of the specification.

Appropriate correction is required.

Claim Objections

Claim 4 is objected to because of the following informalities:

It is missing a period at the end of the claim. Additionally, it is not clear if claim 4 is missing any additional words or lines after "IgG class".

Appropriate correction is required.

Claim Rejections - 35 USC § 112 (Second paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-13, 20-21, 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "at the same degree" in claim 2 is a relative term which renders claims 2-13, 20-21, 29-30 indefinite. The phrase "at the same degree" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For instance, it is not clear how the binding affinities of the antibody binding to IGF-I and IGF-II are related to each other or what strength of binding or binding constant the term is referring to.

The term "biological activities" in claim 1 is a relative term which renders claim 1 indefinite. The term "biological activies" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For instance, it is not clear what specific function(s) of IGF-I and IGF-II are encompassed or referred to by the claims.

The term " represented by " in claims 6-13, 29-30 is a relative term which renders the claims6-13, 29-30 indefinite. The term " represented by " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For instance, it is not clear if the claims are directed to full-length sequences or variants or fragments of the sequences. Please note that this issue could be overcome by amending the claims to recite, for example, "...recombinant antibody or the antibody fragment thereof consist of SEQ ID NOs:...".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 20-21, 29-30 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/513,148. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are drawn to an antibody or antibody fragment, which specifically binds to IGF-I and IGF-II to inhibit functions of human IGF-I and human IGF- and has the binding activity with a binding constant of 5×10^9 M^{-1} or more measured with biosensor BIACORE. The claims of the instant application are drawn to a recombinant antibody or antibody fragment wherein the recombinant antibody or the antibody fragment specifically binds to human insulin-like growth factor-I (IGF-I) and human insulin-like growth factor-II (IGF-II) to inhibit the biological activities of human IGF-I and human IGF-II. In addition, SEQ ID NOs:5-10 of the instant claims are identical to the SEQ ID NOs:5-10 of application 10/513,148. Thus, the antibody of the instant application overlaps in scope with the antibody recited in the application 10/513,148.

In addition, claim 5 of the instant application drawn to the recombinant antibody or the antibody fragment wherein recombinant antibody comprises the complimentarity-determining regions (CDRs) of the of the heavy chain variable region (VH) and light chain variable (VL) of a monoclonal antibody against human IGF encompasses the large genus of antibodies against human IGF. The recitation of claim 5 includes the antibody species disclosed in claims 6 and 8 of application 10/513,148. Claims 6 and 8 are drawn to the antibody or antibody fragment wherein the antibody comprising the amino acid sequence represented by SEQ ID NO:2 and/or VL of the antibody comprising the amino acid sequence encoded by SEQ ID NO:4 are encompassed in the large genus of antibodies against human IGF recited in claim 5 of the

instant application because SEQ ID NO:2 and SEQ ID NO:4 are specific sequence for an antibody against human IGF.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112 (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9-13, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the anti-hIGF rat antibody produced by hybridoma KM1468 (herein after called "the antibody KM1468") comprising the amino acid sequences set forth as SEQ ID No 5, 6, 7, as CDR1, 2, and 3, of the VH region respectively and SEQ ID NO: 8, 9, and 10 as CDR1, 2, 3, of the VL region respectively and the anti-hIGF chimeric antibody produced by hybridoma KM3002 (herein after called "the antibody KM3002) does not reasonably provide enablement for any recombinant antibody or antibody fragment wherein the recombinant antibody or the antibody fragment specifically binds to human insulin-like growth factor-I (IGF-I) and human insulin-like growth factor-II (IGF-II) to inhibit the biological activities of human IGF-I and human IGF-II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of

the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Nature of the invention and breath of the claims

The claims are drawn to a recombinant antibody or antibody fragment wherein the recombinant antibody or the antibody fragment specifically binds to human insulin-like growth factor-I (IGF-I) and human insulin-like growth factor-II (IGF-II) to inhibit the biological activities of human IGF-I and human IGF-II. The claimed antibody also includes several substitutions or deletions in the IGF-I antibody heavy and light chains. The invention is broad because the claims encompasses numerous antibodies with different CDRs composing the light and heavy chain of the antibody.

Unpredictability and state of the art

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor

changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

In addition, Colman (Research in immunology 145:33-36, 1994) teach that example of antigen-antibody interactions paints a confusing picture and a conservative substitution may abolish binding (see page 35). Thus, it is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions or contain conservative substitutions, have the required binding function.
In view of these teachings with respect to amino acid substitutions and deletions in the heavy and light chain of the antibody, any amino acid changes in the sequence encoded an IGF-I antibody are not predictable.

The amount of direction or guidance present

Applicants' disclosure is limited to the characterization for the activities of the anti-hIGF rat antibody KM1468 and the anti-hIGF chimeric antibody KM3002. The specification does not provide guidance or direction regarding how the anti-IGF-I antibodies KM1468 and KM3002 can retain their activities by substitution or deletion of amino acid residues in the CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence while maintaining all of the CDRs of the heavy chain, the light chain or both the heavy and light chains.

The Examiner has interpreted claims 1-7, 9-13, and 20-21 as encompassing a large number of antibodies, since the claims do not recite any specific structural of functional limitations. In addition, the specification does not provide any guidance regarding any specific

functional or structural characteristics for antibodies other than those generated by hybridomas KM1468 and KM3002. For instance, the specification teaches that the recombinant antibody or the antibody fragment thereof of the present invention includes any recombinant antibody or an antibody fragment thereof which specifically binds to hIGF-I and hIGF-II to inhibit the biological activities of hIGF-I and hIGF-II (page 16, 4th paragraph).

Working Examples

Although Applicants have provided a numerous examples for the anti-hIGF rat antibody KM1468 comprising the amino acid sequences set forth as SEQ ID No 5, 6, 7, as CDR1, 2, and 3, of the VH region respectively and SEQ ID NO: 8, 9, and 10 CDR1, 2, 3, of the VL region respectively and the anti-hIGF chimeric antibody KM3002, the specification does not provide any examples for the rat antibody KM1468 or KM3002 with substitutions or deletions in the antibody heavy and light chains as required in claims 9-13. The specification also does not teach any methods or examples directed to other anti-hIGF antibodies, besides KM1468 and KM3002.

The quantity of experimentation needed

Without sufficient disclosure in the specification, it would require undue experimentation for one of skill in the art to make/use the recombinant antibody or antibody fragment binding to human insulin-like growth factor-I (IGF-I) and human insulin-like growth factor-II (IGF-II). In addition, it would require undue experimentation to practice the invention commensurate in scope with the claims because claims 1-7, 9-13, and 20-21 are broadly drawn to a genus of recombinant antibodies or antibody fragments wherein the recombinant antibodies or the antibody fragments specifically bind to human insulin-like growth factor-I (IGF-I) and human

insulin-like growth factor-II (IGF-II) to inhibit the biological activities of human IGF-I and human IGF-II. Also, because Applicant's disclosure does not contain sufficient teachings to overcome the unpredictability taught in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Ben et al., (1991, Growth Regulation, Volume 1, pages 160-167, cited in the IDS filed 10/23/2007).

Ben et al. teach a recombinant antibody binding to IGF-I and IGF-II that inhibit the growth effects of human osteosarcoma cells (page 160, abstract) meeting the limitations of claim 1. In addition, Ben et al. teach that the monoclonal antibody binds to human IGF-I and also binds to human IGF-II (page 160, abstract) meeting the limitations of claim 2.

Conclusion

No claim is allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
October 26, 2007

Bridget E. Bunner

BRIDGET E. BUNNER
PRIMARY EXAMINER